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Melatonin–Dopamine Interactions: From Basic Neurochemistry to a Clinical Setting

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SUMMARY

To review the interaction between melatonin and the dopaminergic system in the hypothalamus and striatum and its potential clinical use in dopamine-related disorders in the central nervous system. Medline-based search on melatonin–dopamine interactions in mammals. Melatonin, the hormone produced by the pineal gland at night, influences circadian and seasonal rhythms, most notably the sleep–wake cycle and seasonal reproduction. The neurochemical basis of these activities is not understood yet. Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla-pons, and retina). Antidopaminergic activities of melatonin have been demonstrated in the striatum. Dopaminergic transmission has a pivotal role in circadian entrainment of the fetus, in coordination of body movement and reproduction. Recent findings indicate that melatonin may modulate dopaminergic pathways involved in movement disorders in humans. In Parkinson patients melatonin may, on the one hand, exacerbate symptoms (because of its putative interference with dopamine release) and, on the other, protect against neurodegeneration (by virtue of its antioxidant properties and its effects on mitochondrial activity). Melatonin appears to be effective in the treatment of tardive dyskinesia, a severe movement disorder associated with long-term blockade of the postsynaptic dopamine D_2 receptor by antipsychotic drugs in schizophrenic patients. The interaction of melatonin with the dopaminergic system may play a significant role in the nonphotic and photic entrainment of the biological clock as well as in the fine-tuning of motor coordination in the striatum. These interactions and the antioxidant nature of melatonin may be beneficial in the treatment of dopamine-related disorders.

KEY WORDS: melatonin; dopamine; Parkinson's disease; tardive dyskinesia; biological clock; circadian rhythms.

INTRODUCTION

All living organisms, from single-celled ones to man, exhibit profound changes in vital homeostatic functions (sleep, wakefulness, temperature, feeding, neuroendocrine, and autonomic rhythms) between states of high and low activity during the 24-h

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day–night cycle (Dunlap, 1999). These cycles are driven by endogenous clocks, with a periodicity approximating to 24 h (circadian), that are adjusted (entrained) to the 24-h periodicity by the daily light–dark cycles. In mammals, including humans, the circadian clock lies in a paired tiny nucleus in the hypothalamus, the suprachiasmatic nucleus (SCN) (Hastings, 1998). The nucleus contains GABAergic neurons and is entrained via a glutamate-dependent pathway by light received by the retina. An important output signal generated by the SCN is the circadian rhythm in production of melatonin (*N*-acetyl-5-methoxytryptamine) in the pineal gland (Reiter, 1991).

Melatonin is produced and secreted at night into the cerebrospinal fluid (CSF) and blood circulation. The neural pathway that extends from the SCN to the pineal gland involves a multisynaptic link via the superior cervical ganglion (SCG) (Ebadi and Govitrapong, 1986). In continuous darkness, melatonin rhythms persist with an SCN-driven circadian periodicity. Light–dark cycles synchronize the rhythm (because of entrainment of the circadian pacemaker) and acute light exposure at night rapidly stops melatonin production (Coon *et al.*, 1995; Gastel *et al.*, 1998). Melatonin undergoes first-pass hepatic metabolism (half-life in the human serum <1 h) (Waldhauser *et al.*, 1984), and its concentrations in the blood, therefore, closely reflect the rate of its synthesis in the pineal. Consequently, the variations in melatonin levels provide the organism with information on the timing and duration of the dark period regardless of the animal being nocturnally or diurnally active (Reiter, 1991).

Apparently, extrapineal melatonin synthesis exists in the mammalian brain and retina. A circadian oscillator located within the retina controls melatonin synthesis in the retina. Retinal melatonin and dopamine appear to act as mutually inhibitory paracrine signals for night and day, respectively (Fujieda *et al.*, 2000; Jaliffa *et al.*, 2000; Tosini and Dirden, 2000). In addition, expression of the key enzyme for melatonin synthesis, arylalkylamino *N*-acetyl transferase, has been demonstrated in the brainstem, midbrain, and hippocampus (Coon *et al.*, 1995), although evidence for the actual production of melatonin at these extrapineal sites has not been demonstrated. The physiological significance of extrapineal melatonin has not been uncovered yet. It may act locally with little contribution, if any, to the circadian rhythm of the hormone in blood.

Melatonin acts as a time cue to entrain or phase shift the endogenous clock in vivo (Lewy *et al.*, 1992). Direct effects of melatonin on SCN firing rate and gene expression have been demonstrated (McArthur *et al.*, 1997). The effects of melatonin on the clock appears to be 180° out of phase with that effected by light exposure (Lewy *et al.*, 1996). Contemporaneous melatonin administration modifies the capability of light to induce circadian phase shifts (Cagnacci *et al.*, 1992; Deacon and Arendt, 1996). Because of these effects melatonin is considered to be potentially useful for treating jet lag and circadian-rhythm–related sleep disorders in the blind and in sighted subjects (Zisapel, 2001).

As a signal of darkness in the organism melatonin has a major role in regulation of sleep (Lockley *et al.*, 1997). The sleep-inducing activity of melatonin is best demonstrable during the day time or under conditions in which endogenous production is low (Cajochen *et al.*, 1996; Garfinkel *et al.*, 1995; Young, 1996). The ability of melatonin to increase sleep propensity makes it a reasonable therapeutic candidate for

insomnia in elderly who have low endogenous production of the hormone (Zisapel, 1999). Concomitantly, and perhaps causally related, to the sleep-inducing activity of melatonin, it also enhances distal vasodilation in humans, resulting in heat loss and lowering of core body temperature (Cagnacci *et al*., 1992; Krauchi *et al*., 2000). In addition, melatonin mediates the induction or suppression of reproduction, as a result of exposure to short-day photoperiods in seasonal breeders (Reiter, 1991). In rats, and possibly in humans, melatonin delays the onset of puberty (Rivest *et al*., 1986; Waldhauser *et al*., 1991).

Understanding the neurochemical basis of melatonin action may provide a basis for a better understanding of its physiological activity and potential clinical use. This review will focus on the effects of melatonin on dopaminergic mechanisms in the hypothalamus and striatum and their potential clinical implications.

Inhibition by Melatonin of Dopamine Release

An inhibitory effect of melatonin on stimulated dopamine release was first demonstrated in excised female rat hypothalamic tissue in vitro (Zisapel and Laudon, 1982). Inhibition of dopamine release was also observed in the rat ventral hippocampus but not in the cerebral cortex, cerebellum, dorsal hippocampus, and striatum (Zisapel *et al*., 1982). Inhibition was significant at nanomolar concentrations of melatonin, considered to be physiologically relevant, and was maximal at micromolar concentrations of melatonin. The inhibition by melatonin of stimulated dopamine release appears to be caused by suppression of calcium influx into the stimulated nerve endings (Zisapel and Laudon, 1983).

Evidence in vivo supports the in vitro findings on modulation of dopamine release by melatonin in hypothalamic areas. DOPAC and DOPA levels in the rat median eminence, used as indicators of the dopamine-releasing activity of the terminal regions of the tuberoinfundibular and nigrostriatal dopaminergic neurons, exhibited significant diurnal variations with low levels in the late afternoon (1700–2100 hours), and higher levels during the dark (2100–0500 hours) phase. The late afternoon decline in median eminence DOPA was abrogated by continuous light, and could be reinstated by exogenous melatonin administration (Shieh *et al*., 1997). Notably, the inhibition by melatonin of stimulated dopamine release from the male rat hypothalamus in vitro also exhibited a 24-h rhythm, with a peak at 5 h after lights-on and almost no inhibition 10 h later in the day (Zisapel *et al*., 1985). Studies in vivo using microdialysis methods demonstrated an inhibitory effect of melatonin on amphetamine-induced release of dopamine from the rat mediobasal hypothalamus. Inhibition of dopamine release was associated with a significant increase in glutamate and aspartate release in young but not middle-aged or aged rats (Exposito *et al*., 1995).

In the male Syrian hamster daily late afternoon administration of melatonin for 9 weeks resulted in a progressive decline in dopamine content of the posterior pituitary to <50% after 5 weeks of treatment (Alexiuk and Vriend, 1993), suggesting a decrease in tuberoinfundibular dopaminergic neuron activity. Accordingly, the melatonin treatment resulted in a highly significant increase in the in situ activity

of tyrosine hydroxylase (a key enzyme in catecholamine synthesis) in the median eminence/arcuate region of the mediobasal hypothalamus, compared with saline-treated controls. Melatonin-induced elevations in tyrosine hydroxylase occurred concomitantly with a decrease in tuberoinfundibular and tuberohypophyseal dopamine concentrations (Alexiuk *et al*., 1996).

In the ewe, photoperiod and melatonin decreased hypothalamic dopamine content in the median eminence, suggesting that melatonin mediates the effect of short days on this activity (Viguie *et al*., 1997). In addition, in anestrous ewes under increasing–day-length conditions, melatonin evoked an abrupt decrease in the concentrations of dopamine in mediobasal hypothalamic perfusates (Misztal *et al*., 1997).

Effects of Melatonin on Striatal Neurons

The dopaminergic nerve endings in the hypothalamus are mainly derived from nigrostriatal and tuberoinfundibular neurons. Therefore, while presynaptic effects of melatonin on dopamine release were mostly demonstrable in the hypothalamus, it is to be expected that the decrease in calcium entry will translate into metabolic changes in the dopaminergic neurons and, among other effects, could reduce their response to stimuli. The nigrostriatal dopaminergic neurons affect inhibitory (D2-receptor–mediated) and stimulatory (D1-receptor–mediated) pathways in the striatum, leading to coordination of motor functions. In the striatum, glutamate mediates excitatory responses to motor cortex stimulation (Cote and Crutcher, 1991). Iontophoresis of melatonin attenuated the glutamate-dependent excitatory response to motor cortex stimulation in striatal neurons in the rat (Escames *et al*., 1996). Sulpiride (a D2 antagonist) produced an immediate increase in the excitatory response of striatal neurons and counteracted melatonin's effect (Escames *et al*., 1996), compatible with the effects of melatonin on dopaminergic pathways. As in the hypothalamus (Zisapel and Laudon, 1983), the effects of melatonin on striatal neurons were due to a decreased influx of calcium into the stimulated cells (Escames *et al*., 2001). The antidopaminergic effects of melatonin in the striatum may also involve GABA-ergic transmission (Tenn and Niles, 1997). Melatonin also suppresses nitric oxide synthase activity in the rat striatum, an effect that is compatible with suppression of *N*-Methyl-D-Aspartate(NMDA)-type glutamate receptors (Leon *et al*., 1998). Figure 1 represents a hypothetical schematic diagram to explain the effects of melatonin on neurotransmission in the striatum. It may be proposed that melatonin attenuates dopamine release in the striatum, by the nigrostriatal system (Escames *et al*., 1996; Exposito *et al*., 1995). In addition melatonin suppresses postsynaptic NMDA-receptor–mediated responses of striatal neurons to glutamate. Notably, dopamine not only modulates the postsynaptic potential of striatal neurons, but may also modulate NMDA receptors involved in long-term potentiation and perhaps depression of corticostriatal glutamate synapses (Di Chiara *et al*., 1994). Therefore, an antidopaminergic effect of melatonin in the striatum may also modulate striatal neurons' responses to glutamate. As a result, the release of GABA from the striatum may be suppressed, giving rise to disinhibition of downstream pathways and of the nigrostriatal neurons. In the rat striatum, melatonin did not have a considerable effect on

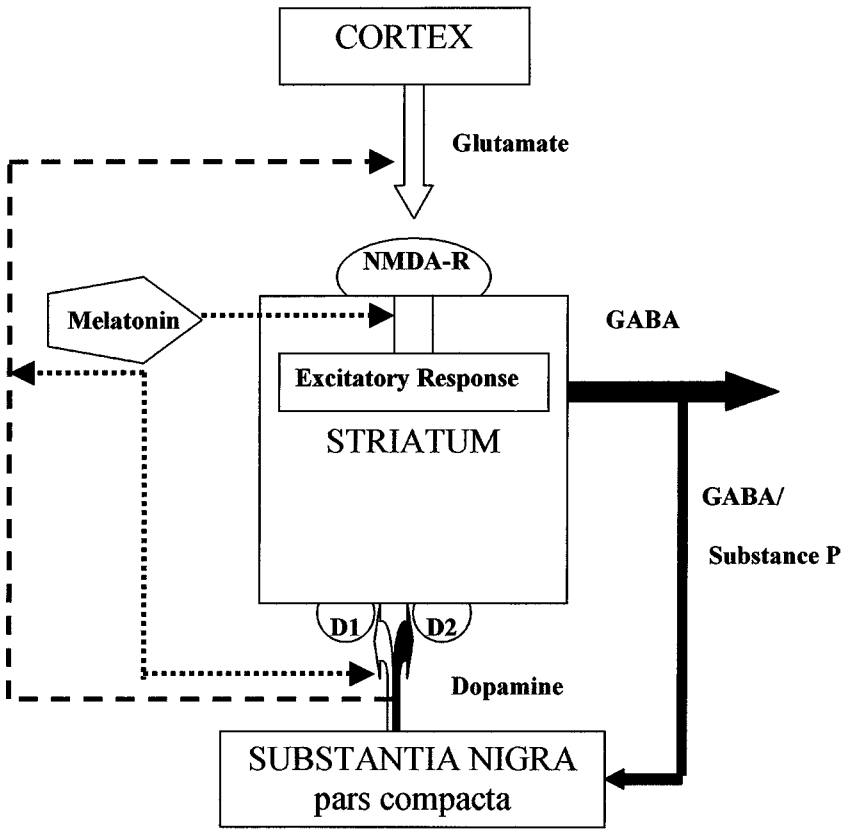

Fig. 1. A schematic diagram of the effects of melatonin on the main neurotransmitter systems connected to the striatum. Black arrows represent inhibitory connections; white arrows represent excitatory connections. (Adapted from Cote and Crutcher, 1991). Striated arrows represent inhibitory effects of melatonin. NMDA-R, D1, and D2 denote specific subtypes of the melatonin, glutamate, and dopamine receptors, respectively.

stimulated dopamine release in vitro (Zisapel *et al.*, 1982), perhaps because of the complex nature of neuronal circuitry in this brain region.

Melatonin Receptors in the Brain and Their Involvement in Modulation of Dopamine Release

In mammals, two types of high-affinity membranal melatonin receptors have been cloned, mt_1 (also termed mel_{1a}) and MT_2 (mel_{1b}) (Reppert, 1997), that belong to the seven transmembrane G-protein–coupled receptors superfamily. Both subtypes are expressed in the SCN but only one (mt_1) displays demonstrable iodomelatonin binding in this region. In addition, nuclear receptors and binding to ubiquinone reductase have been described, but their activation or inhibition by melatonin is plausible (Nosjean *et al.*, 2000). The relationship between the cloned melatonin

receptors and the biological activities of melatonin is not well understood. In knockout mice that do not express the mt_1 melatonin receptors, the acute suppression of the firing rate of SCN neurons by melatonin was abolished, but melatonin was still able to phase shift the rhythm in SCN firing rate in vitro (Liu *et al*., 1997). This implicates the mt_1 receptors in the acute suppression of SCN electrical activity but not the phase-shifting effects of melatonin. Indirect pharmacological evidence has implicated MT_2 melatonin receptors in the phase-resetting activity of melatonin (Hunt *et al*., 2001). However, in Syrian hamsters lack of expression of MT_2 is not associated with problems in circadian entrainment or photoperiodic responsiveness (Weaver *et al*., 1996).

The inhibition by melatonin of stimulated dopamine release from the hypothalamus appears to be mediated by membranal, low-affinity (Kd for iodomelatonin 40 nM) melatonin binding sites via suppression of calcium influx into the stimulated nerve endings (Laudon and Zisapel, 1986; Zisapel and Laudon, 1983). The effects of melatonin on glutamate-induced excitation of striatal neurons and calcium influx in the striatum have a similar dose-response dependency (Escames *et al*., 2001). In the mature rat, the specific low-affinity binding of [^{125}I]-labeled iodomelatonin (^{125}I-melatonin) was found in the hypothalamus, medulla-pons, hippocampus, cerebellum, parietal cortex, and striatum. These findings support a role for low-affinity melatonin target sites in the brain. Recent data obtained from sheep indicate that melatonin concentrations in the CSF, particularly in the third ventricle, may exceed those in the circulation by several times (Rousseau *et al*., 1999). A similar finding was reported earlier in calves (Hedlund *et al*., 1977). It is interesting to note that some of the melatonin-responsive areas partially coincide with sites that have the capacity to produce melatonin (Coon *et al*., 1995), so that local concentrations of the hormone in them may be even higher. Hence, it is reasonable to assume that some of the neurochemical effects of melatonin in the brain, including the regulation of sleep, are mediated by additional—as yet unidentified—receptors that have a lower affinity for melatonin and would only be active at levels that exist in the brain at night. This possibility warrants further investigation.

Relevance of the Melatonin–Dopamine Interaction in the Mediobasal Hypothalamus to the Regulation of Prolactin Secretion

Because of the role of tuberoinfundibular dopamine in suppression of prolactin secretion, the relevance of the hypothalamic dopamine-melatonin interaction to pituitary prolactin release has gained much scientific attention. However, studies in sheep and hamsters indicate that the pineal melatonin signal, which transduces the photoperiod effect, acts at brain sites to regulate seasonality in gonadotrophin secretion by the pituitary gland and in sites outside the brain, presumably the pars tuberalis or pituitary gland, to regulate prolactin secretion (Lincoln, 1999; Misztal *et al*., 1997; Viguie *et al*., 1997). In humans, administration of melatonin during daylight hours stimulated growth hormone release, while there was no significant effect on prolactin or cortisol release. (Forsling *et al*., 1999). Hence, a melatonin-mediated suppression of dopamine release in the hypothalamus may not be important in the regulation of prolactin release.

Relevance of Melatonin–Dopamine Interaction in the Hypothalamus to the Regulation of the Biological Clock

In fetal rats and Syrian hamsters, maternal cues entrain a circadian pacemaker. Dopaminergic activation and melatonin may mimic separate but complementary maternal entraining signals that represent day and night. In the Syrian hamster, injection of the dopamine D1 agonist SKF38393 to pregnant hamsters entrained activity rhythms of their pups and induced expression of c-fos in the fetal and neonatal SCN. The phase established by dopaminergic activation was approximately opposite to that established by melatonin injections. These entraining effects of dopaminergic activation were lost by postnatal day 6 (Grosse and Davis, 1999). Pinealectomy of female rats at day 7 of pregnancy resulted in down-regulation of dopamine D1 receptor binding exclusively in the fetuses (embryonic day 21) SCN and up-regulation in the offspring (postnatal day 3 and after) as well as in the mothers SCN. In parallel, melatonin binding was up-regulated in the fetuses and offspring as well as in their pinealectomized mothers' SCN (Naitoh *et al*., 1998). Notably, the inhibition of stimulated dopamine release from the male rat hypothalamus in vitro by melatonin developed in the rat during the first week of life, reaching a plateau level between 6 and 7 days postnatally. From the time inhibition was first observed, the effect of melatonin on dopamine release exhibited a 24-h rhythm with a peak in the early light hours and almost no inhibition before lights off. These developmental changes were accompanied by diurnal changes in density of low-affinity binding sites in the hypothalamus (Zisapel *et al*., 1985; Zisapel *et al*., 1988). In humans evidence for the importance of dopaminergic transmission in the circadian system is still lacking. However, it is interesting to note that prolonged inhibition of presynaptic catecholamine synthesis with α-methyl-para-tyrosine attenuates the circadian rhythm of human TSH secretion (Zimmermann *et al*., 2001). It may be speculated (Fig. 2) that in the SCN melatonin inhibits dopamine release, and perhaps postsynaptic NMDA-receptor–mediated responses to the light signal from the retina, while the SCN modulates the sensitivity of the dopaminergic neurons to melatonin, perhaps via GABAergic transmission. In addition, melatonin may directly inhibit the SCN electrical firing rate (mt_1-receptor–mediated). Thus, as is the case in the retina, melatonin and dopamine act as mutually inhibitory signals for night and day, respectively. The dopaminergic system may participate in entrainment of the biological clock by nonphotic time cues, including melatonin.

Relevance of Melatonin–Dopamine Interaction in the Striatum to the Treatment of Parkinson's Disease and Tardive Dyskinesia

The striatum is primarily involved in motor planning and motor learning. Human diseases involving its complex circuitry result in movement disorders: Parkinson's disease (PD), Huntington's disease (HD), and tardive dyskinesia (TD). While the physiological role of the melatonin–dopamine interaction in the striatum has yet to be elucidated, its implications in the treatment of movement disorders related to the striatal dopaminergic system are pertinent.

PD is a progressive disorder of the central nervous system, caused by striatal deficiency of dopamine following the degeneration of dopaminergic neurons in the

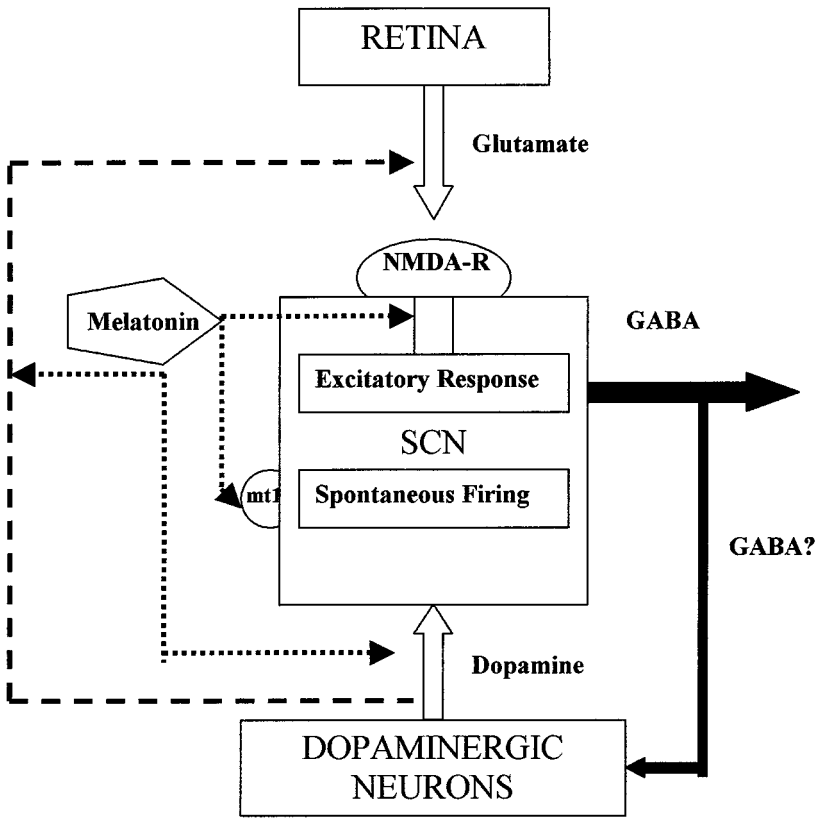

Fig. 2. A schematic diagram of the effects of melatonin and dopamine on the SCN. Black arrows represent inhibitory connections; white arrows represent excitatory connections. Dotted arrows represent inhibitory effects of melatonin. Mt1, NMDA-R, and D1 denote specific subtypes of the melatonin, glutamate, and dopamine receptors, respectively.

substantia nigra of the midbrain. It affects approximately 1% of people after the age of 50. The major symptoms are tremor, rigidity, and bradykinesia. A proportion of PD disease patients show a deficiency in mitochondrial respiratory chain function, in particular a defect in complex I, within neurons of the substantia nigra. This deficit could conceivably contribute to cell death in parkinsonism, both directly via reactive oxygen species production and by decreased ATP synthesis and energy failure (Schapira, 2001). Since melatonin is one of the most potent endogenous scavengers of toxic oxygen radicals, its ability to rescue dopaminergic neurons from damage/death has been extensively investigated. There is substantial behavioral and histochemical evidence showing that melatonin has neuroprotective effects on the nigrostriatal dopaminergic system in several laboratory models associated with oxidative stress, including neurotoxic injury from 1-methyl-4-phenylpyridine (MPP+) and 6-hydroxydopamine (6-OHDA). Analysis of mitochondrial oxidative phosphorylation enzyme activities in nigral tissue from 6-OHDA-lesioned rats revealed a clear protection of mitochondrial Complex I activity by melatonin. These data suggests

that melatonin may be useful as a prophylactic or as a neuroprotective agent to prevent further cell death in an oxidative-stress–induced neurodegenerative disease such as PD (Dabbeni-Sala *et al.*, 2001; Joo *et al.*, 1998; Kim *et al.*, 1998; Ortiz *et al.*, 2001). However, a reduction by melatonin in nigrostriatal dopaminergic activity could theoretically lead to worsening of parkinsonian symptoms, as is indeed suggested by findings in animal models of PD (Willis and Armstrong, 1999). Therefore, melatonin may be beneficial for neuroprotection against further loss of striatal neurons but may potentially exacerbate motor dysfunction in patients who have already developed the disease.

TD is a syndrome of hyperkinetic involuntary movements characterized by a variable mix of orofacial dyskinesia, tics, chorea, and/or athetosis. Blockade of the postsynaptic dopamine D_2 receptor by antipsychotic medications, a common practice in the treatment of psychosis in schizophrenia, is associated with increased prevalence of TD. The pathophysiology of TD remains unclear, although both dopamine receptor supersensitivity (Cardoso and Jankovic, 1997) and oxidative-stress–induced neurotoxicity in the nigrostriatal system are apparently implicated (Barak *et al.*, 1998; Pai *et al.*, 1994; Post *et al.*, 1998). Antioxidants, specifically vitamin E, have been studied as possible agents for both the treatment and prevention of TD (Barak *et al.*, 1998), but their long-term efficacy has been questioned (Adler *et al.*, 1998).

Pineal calcification and low endogenous melatonin levels have been associated with TD in untreated as well as antipsychotic-treated patients with schizophrenia (Rao *et al.*, 1990; Vigano *et al.*, 2001). Melatonin has a potential clinical efficacy in TD because of its antioxidant properties as well as its dopaminergic modulating activities. In an initial double-blind, placebo-controlled, crossover study (Shamir *et al.*, 2000), 19 patients with schizophrenia suffering from TD were randomly assigned to either melatonin (2 mg/day, prolonged release formulation) or placebo for 4 weeks. The primary efficacy outcome was improvement in TD phenotype measured by Abnormal Involuntary Movement Scale (AIMS) score. There was no significant treatment effect by melatonin over placebo in change from baseline in AIMS score, suggesting that doses of melatonin that induce sleep in humans are not efficacious for TD (Shamir *et al.*, 2000). In a subsequent double-blind, placebo-controlled, crossover study, the effect of a higher melatonin dose (10 mg/day, prolonged release formulation) given for a longer period (6 weeks) on TD was evaluated in 22 patients with schizophrenia suffering from TD. The decrease in total AIMS score from baseline (or washout) values was significantly higher with melatonin treatment compared with placebo. A clinically significant outcome, defined as a reduction in total AIMS score greater than 3 points (Adler *et al.*, 1998) was found in seven patients during the melatonin treatment compared with only one during placebo treatment (Shamir *et al.*, 2001).

Because TD is proposed to be associated with dopamine receptor supersensitivity (Cardoso and Jankovic, 1997), the beneficial effects of melatonin in TD may be explained by its inhibitory effect on dopamine release. However, given the brevity of the current investigation, we cannot rule out the possibility that some neuroprotection might also be involved. The potential use of melatonin for treatment of striatal-neuron–based disorders warrants further investigations exploring its mode of action and evaluating potential benefits and risks.

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